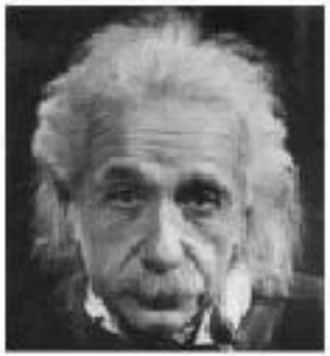
Mitochondria and Aging

Toren Finkel
Center for Molecular Medicine
NHLBI, NIH

Why should we study aging?

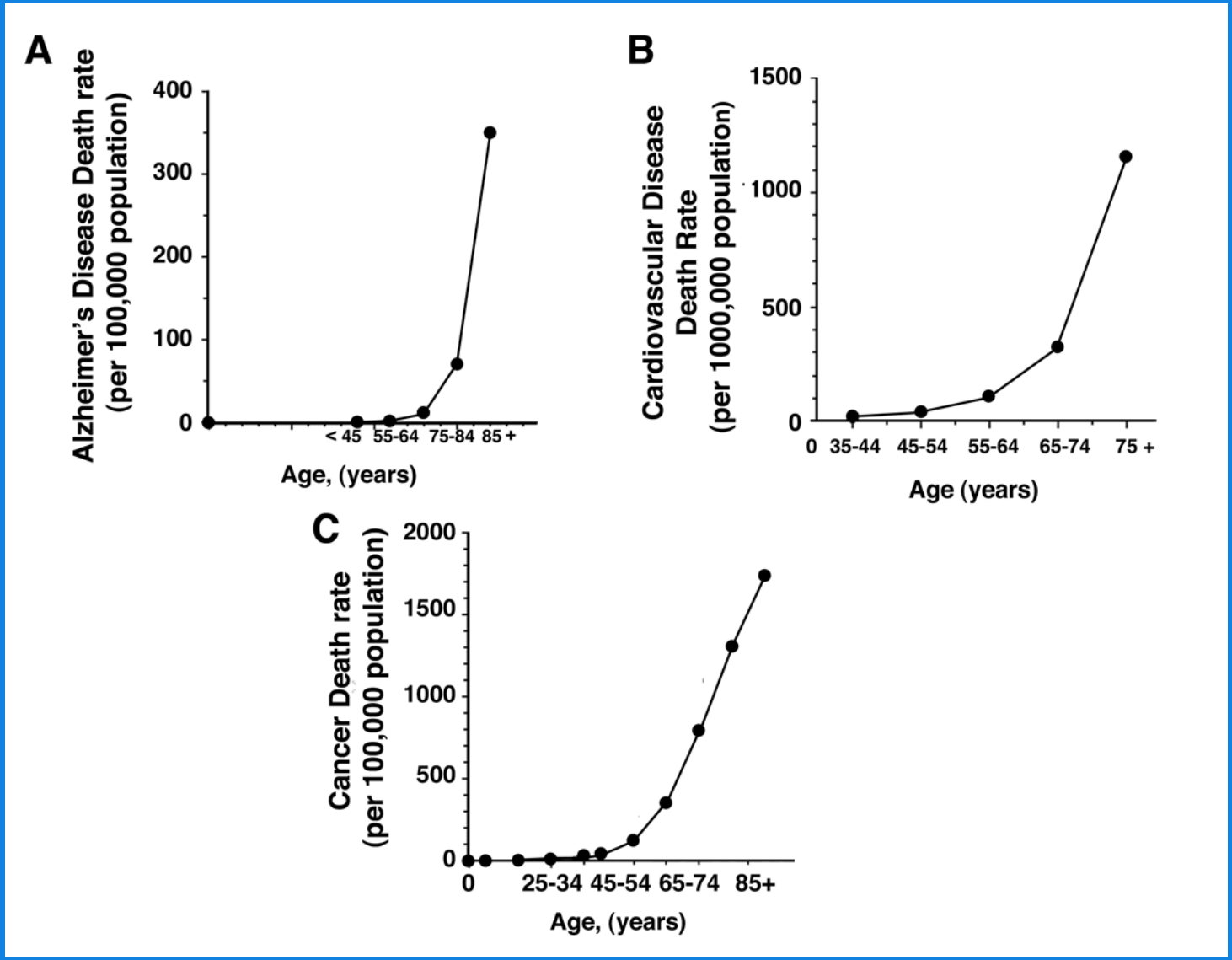
32

52



76

Age-related incidence of major diseases

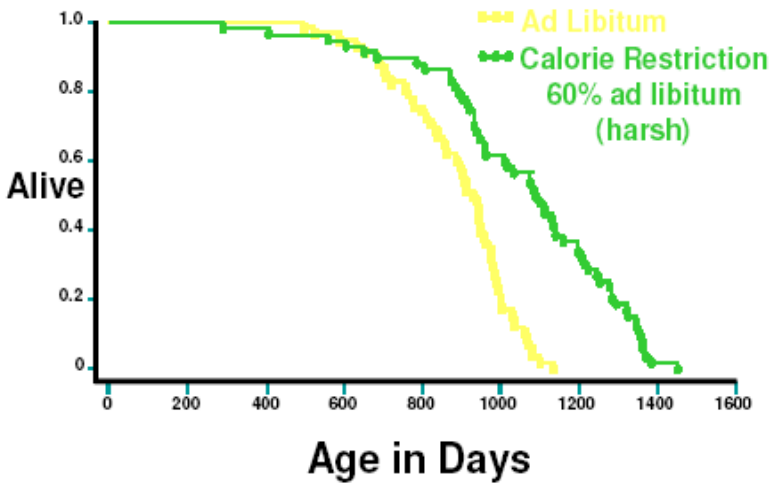


Finkel, *Nat Rev Mol Cell Biol.* (2005)

The world's oldest person: Jeanne Calment

The secret to her longevity?

Calorie restriction extends lifespan universally



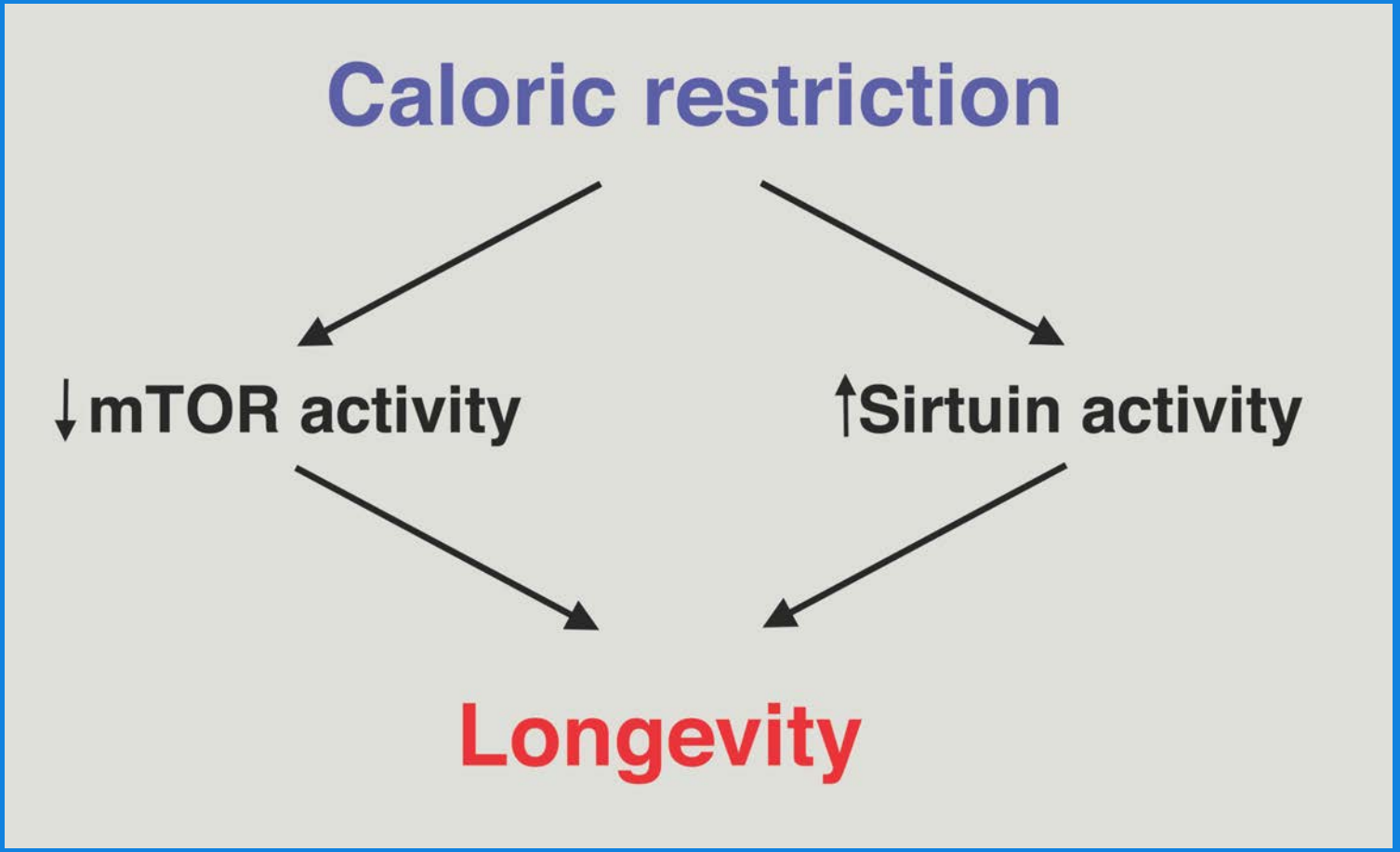
MICE
RATS
FLIES
WORMS
YEAST

KNOWN FOR 70+ YEARS.

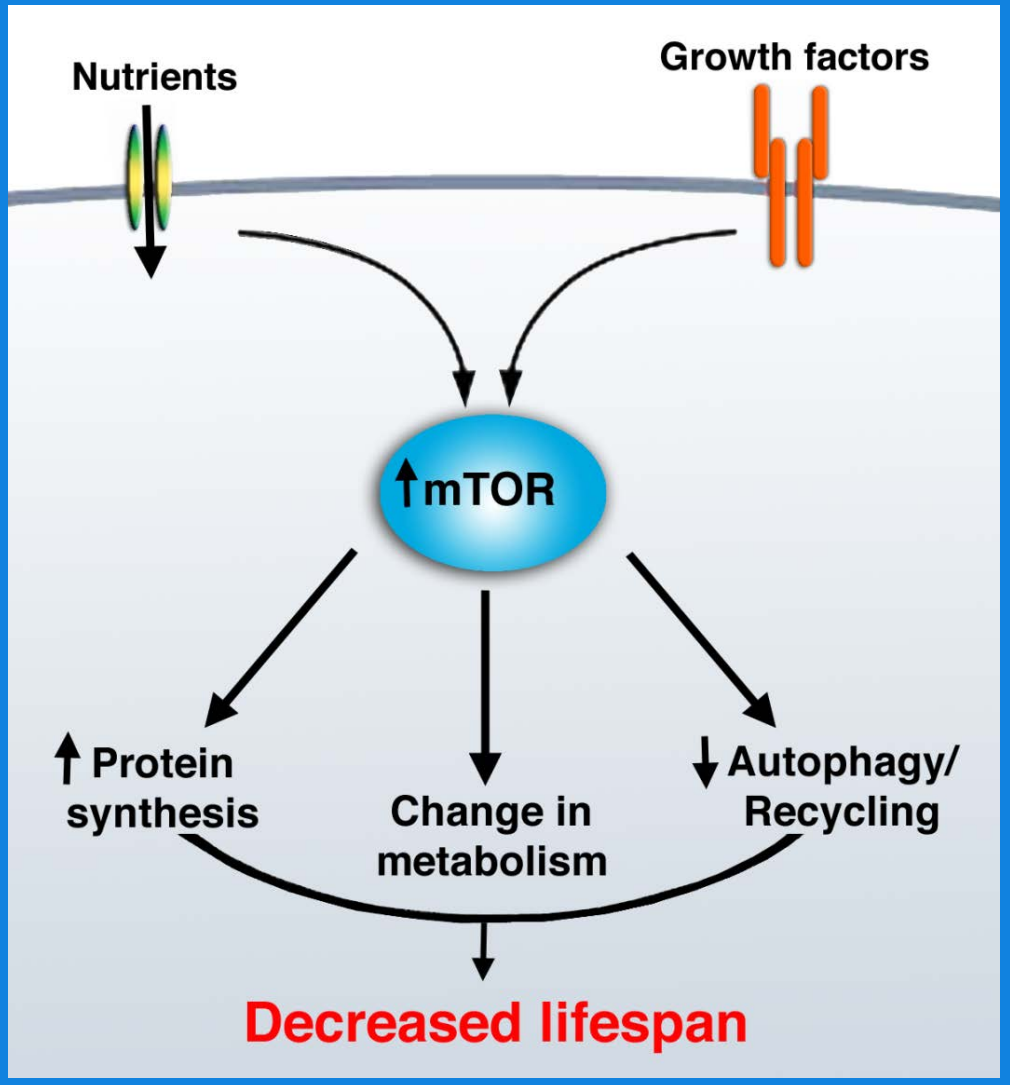
HOW DOES IT WORK?

Data from Arlan Richardson

Two pathways that link CR and lifespan



The mTOR pathway links nutrients to lifespan



A pill to live longer?

nature

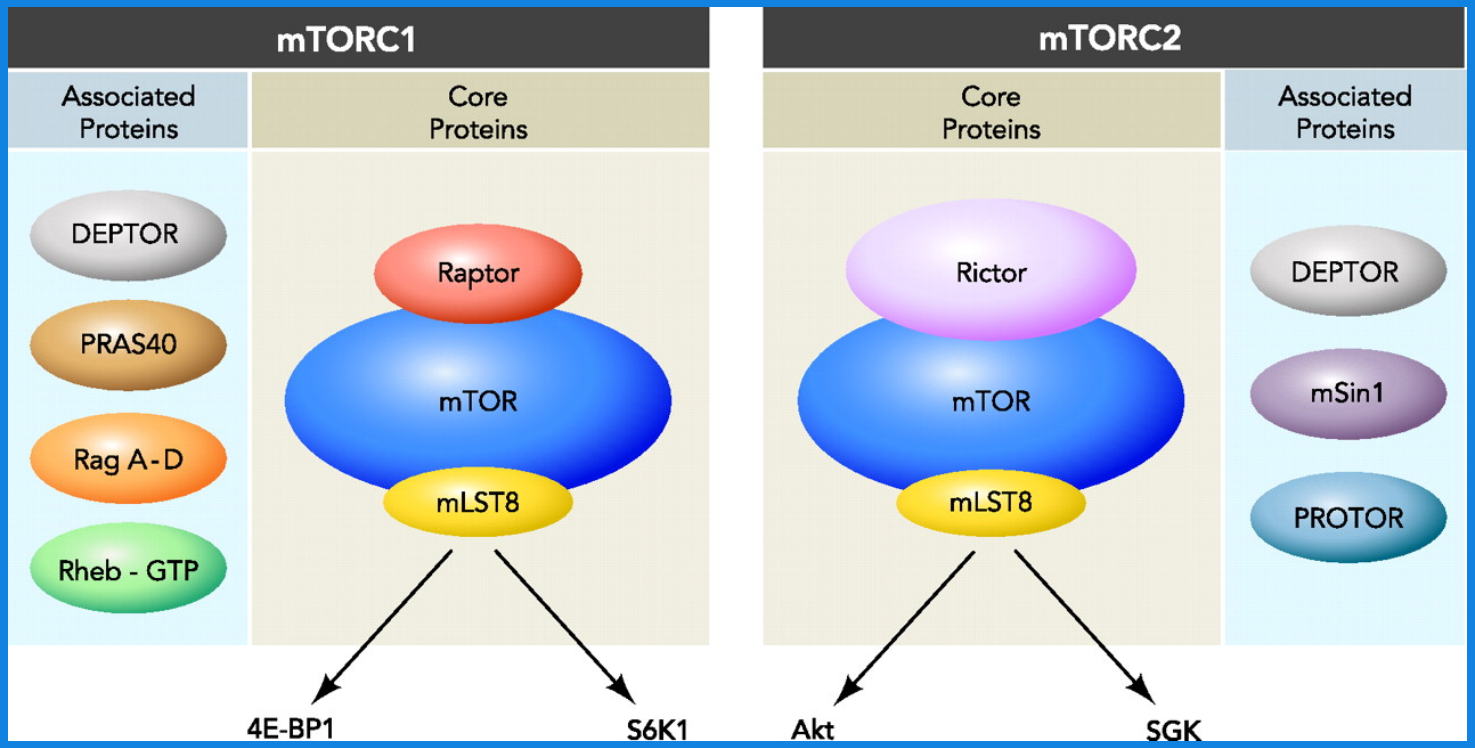
Vol 460|16 July 2009|doi:10.1038/nature08221

LETTERS

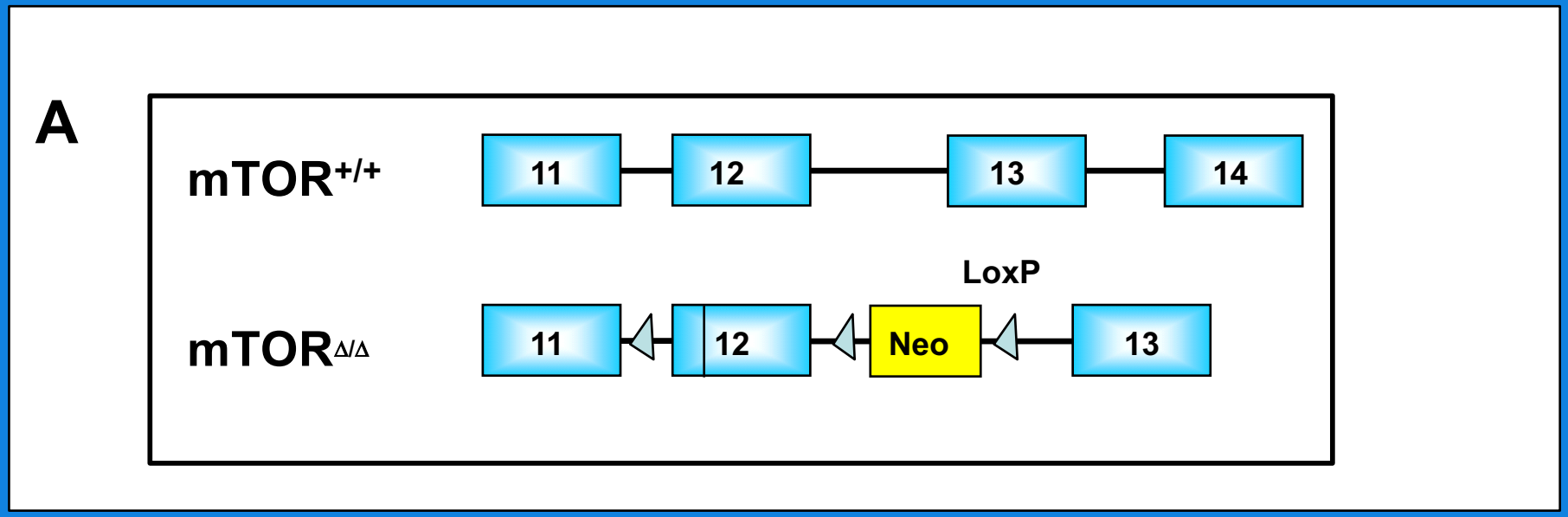
Rapamycin fed late in life extends lifespan in genetically heterogeneous mice

David E. Harrison[1]*, Randy Strong[2]*, Zelton Dave Sharp[3], James F. Nelson[4], Clinton M. Astle[1], Kevin Flurkey[1], Nancy L. Nadon[5], J. Erby Wilkinson[6], Krystyna Frenkel[7], Christy S. Carter[8]†, Marco Pahor[8]†, Martin A. Javors[9], Elizabeth Fernandez[2] & Richard A. Miller[10]*

Knockouts of mTORC1 components are embryonic lethal

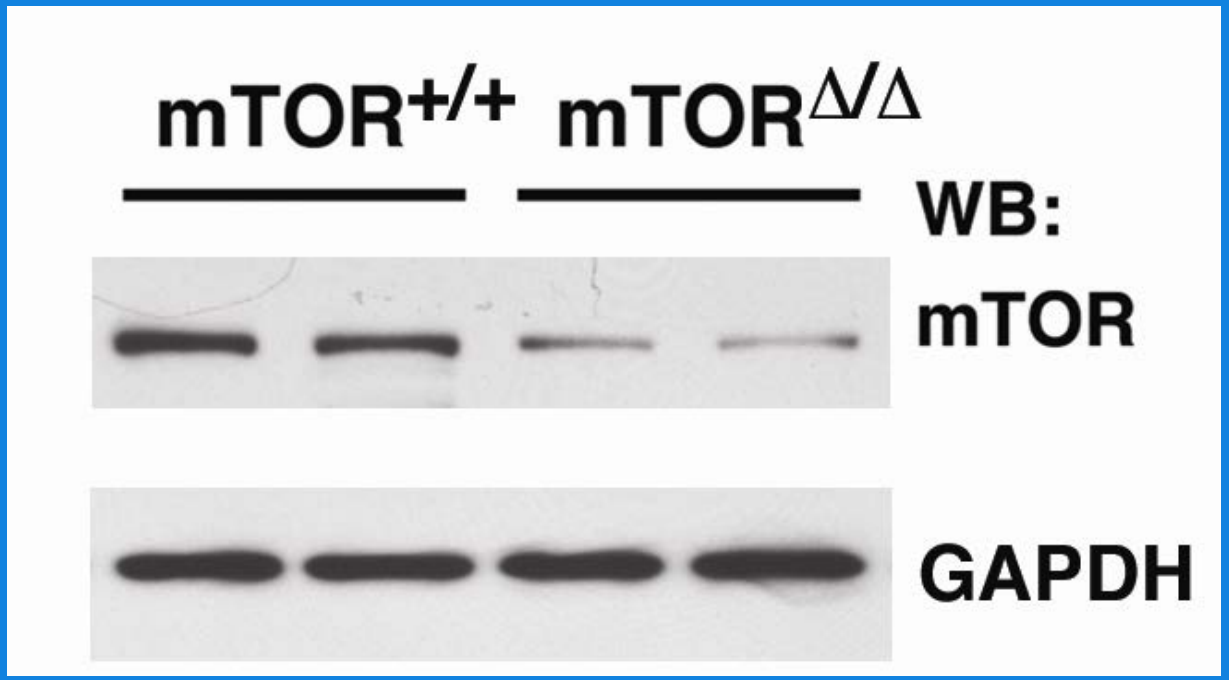


Mouse model to reduce mTOR expression ($mTOR^{\Delta/\Delta}$)



B. Mock (NCI)

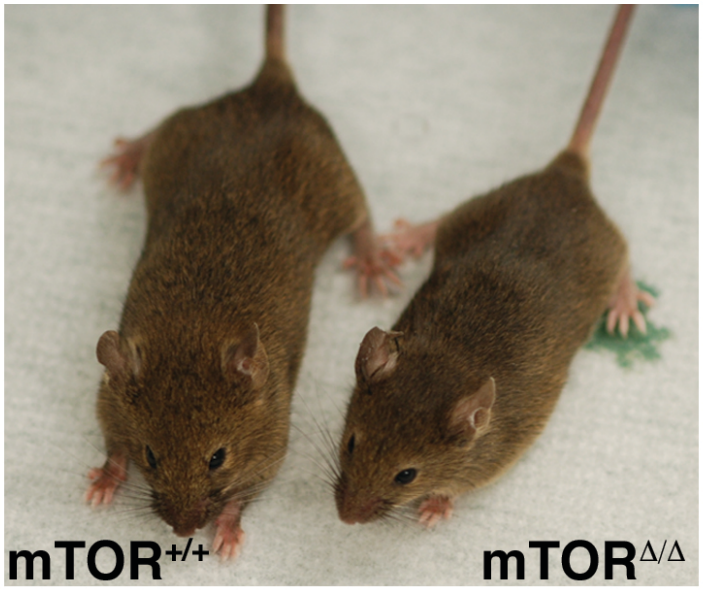
$mTOR^{\Delta/\Delta}$ mice have reduced mTOR expression



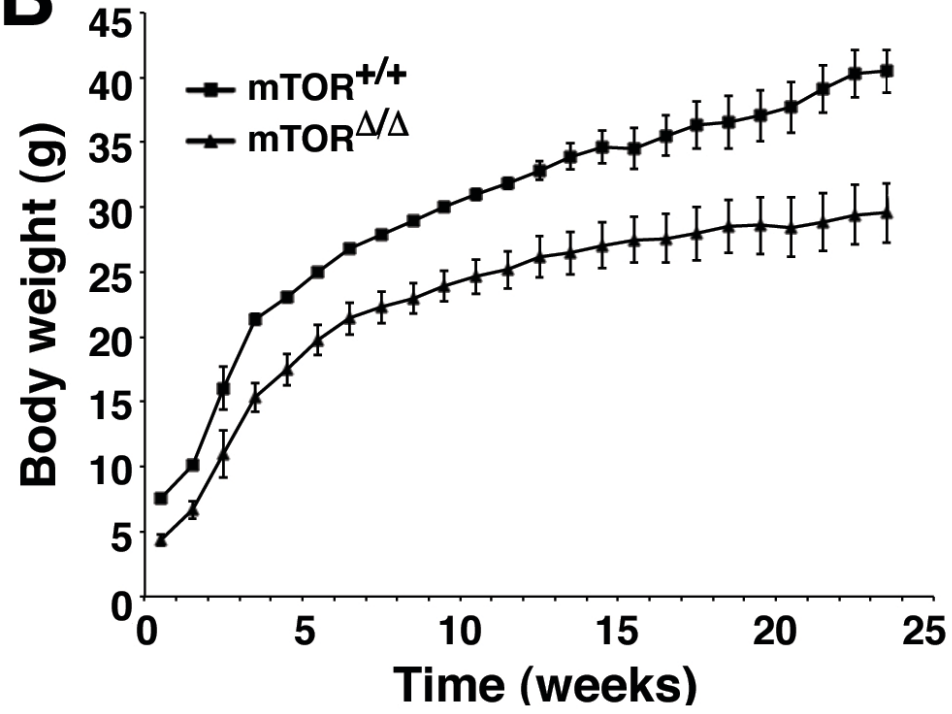
Wu et al., *Cell Reports* (2013)

$mTOR^{\Delta/\Delta}$ mice are small

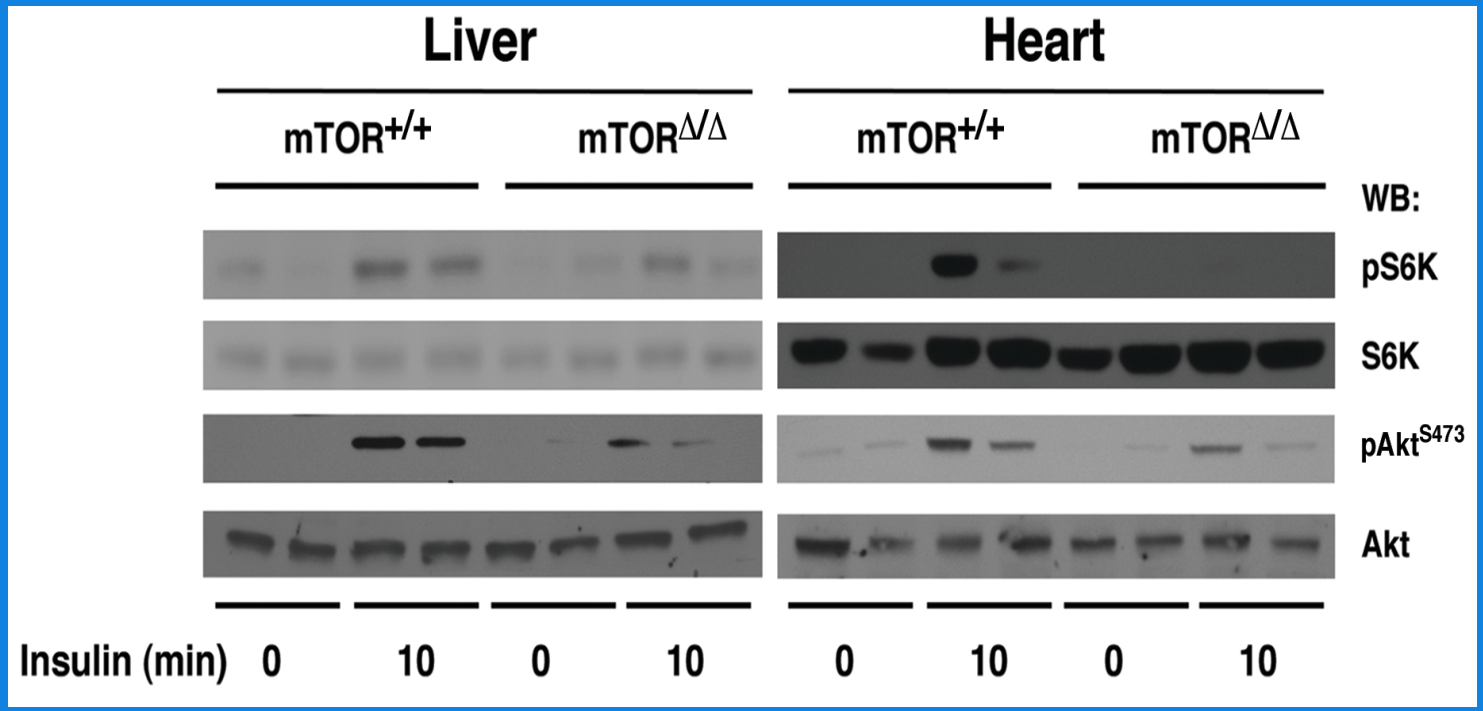
A



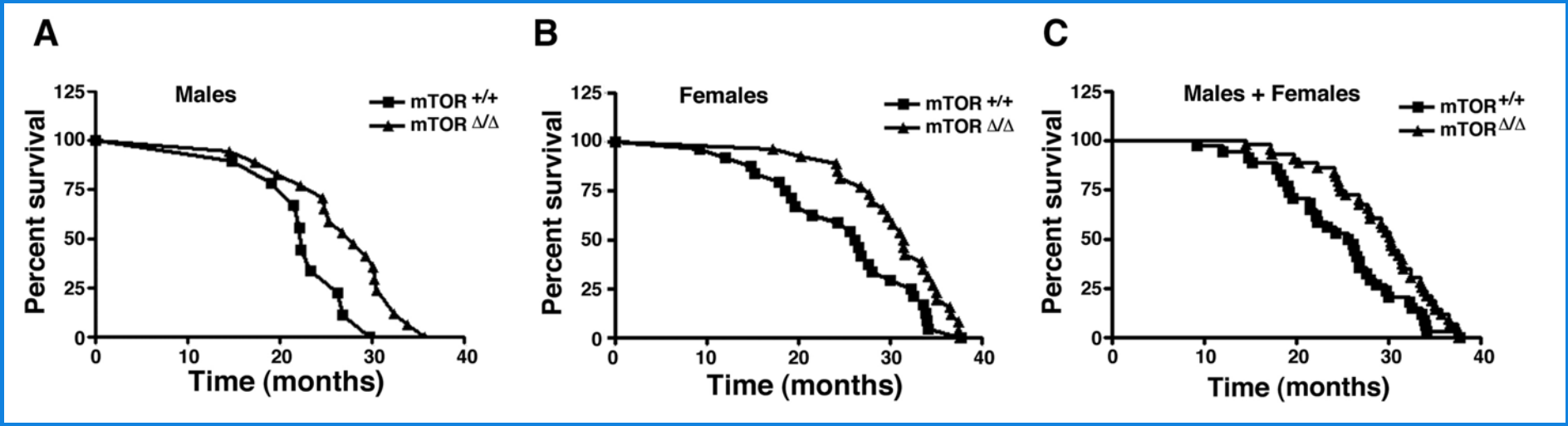
B



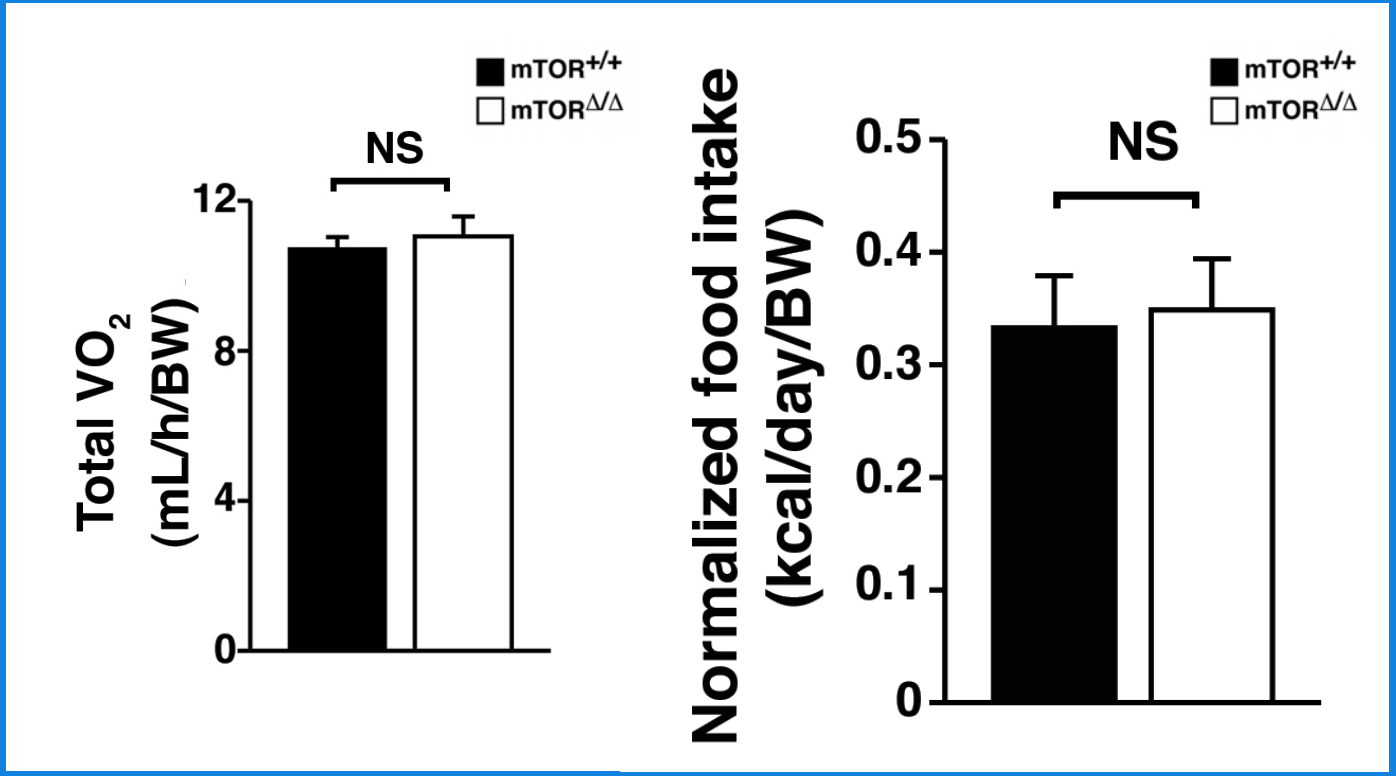
Reduced *in vivo* TORC1 and TORC2 signaling in mTOR$^{\Delta/\Delta}$ mice



$mTOR^{\Delta/\Delta}$ mice have increased life span

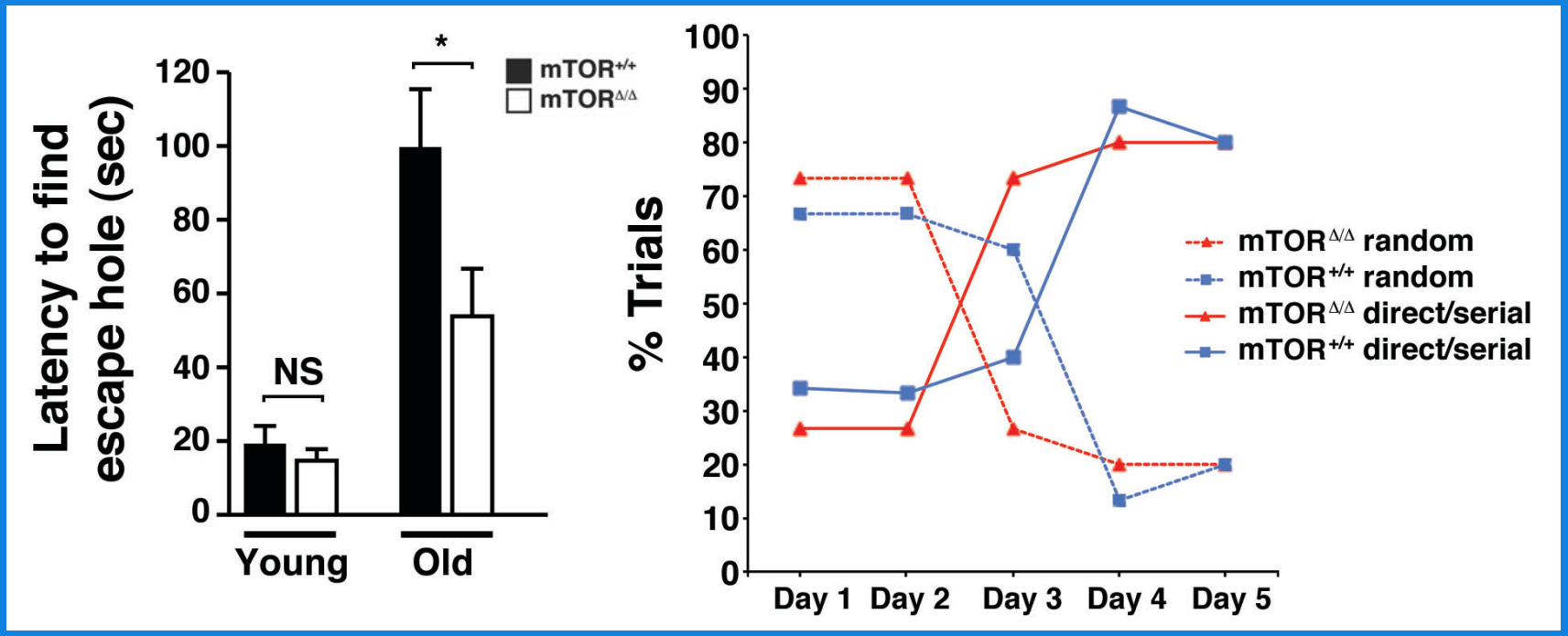


No change in normalized food intake or metabolism in mTOR$^{\Delta/\Delta}$ mice

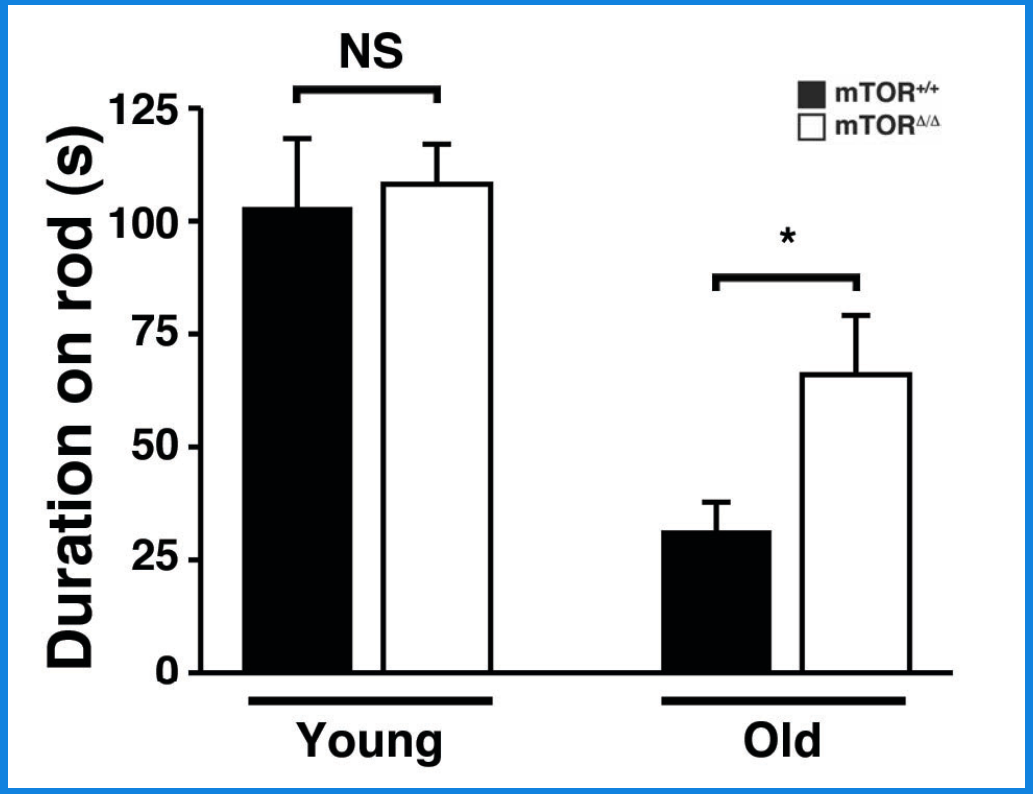


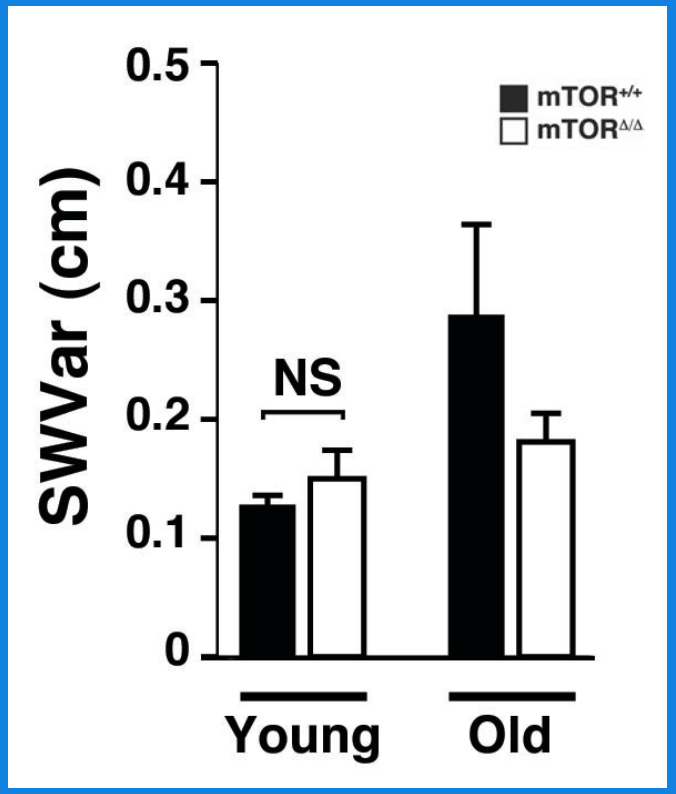
Do mTOR$^{\Delta/\Delta}$ mice age slower?

$mTOR^{\Delta/\Delta}$ mice have preserved age-dependent memory and learning function

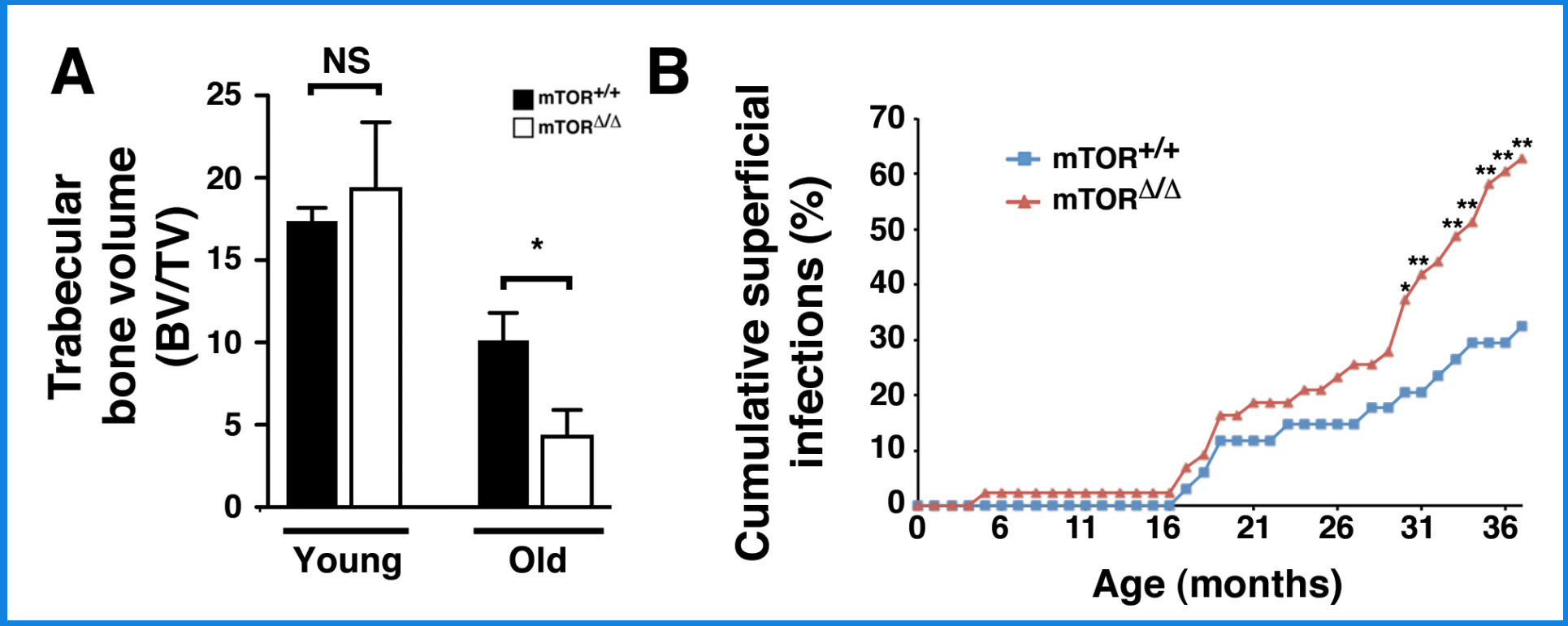


$mTOR^{\Delta/\Delta}$ mice have reduced age-dependent declines in coordination and gait

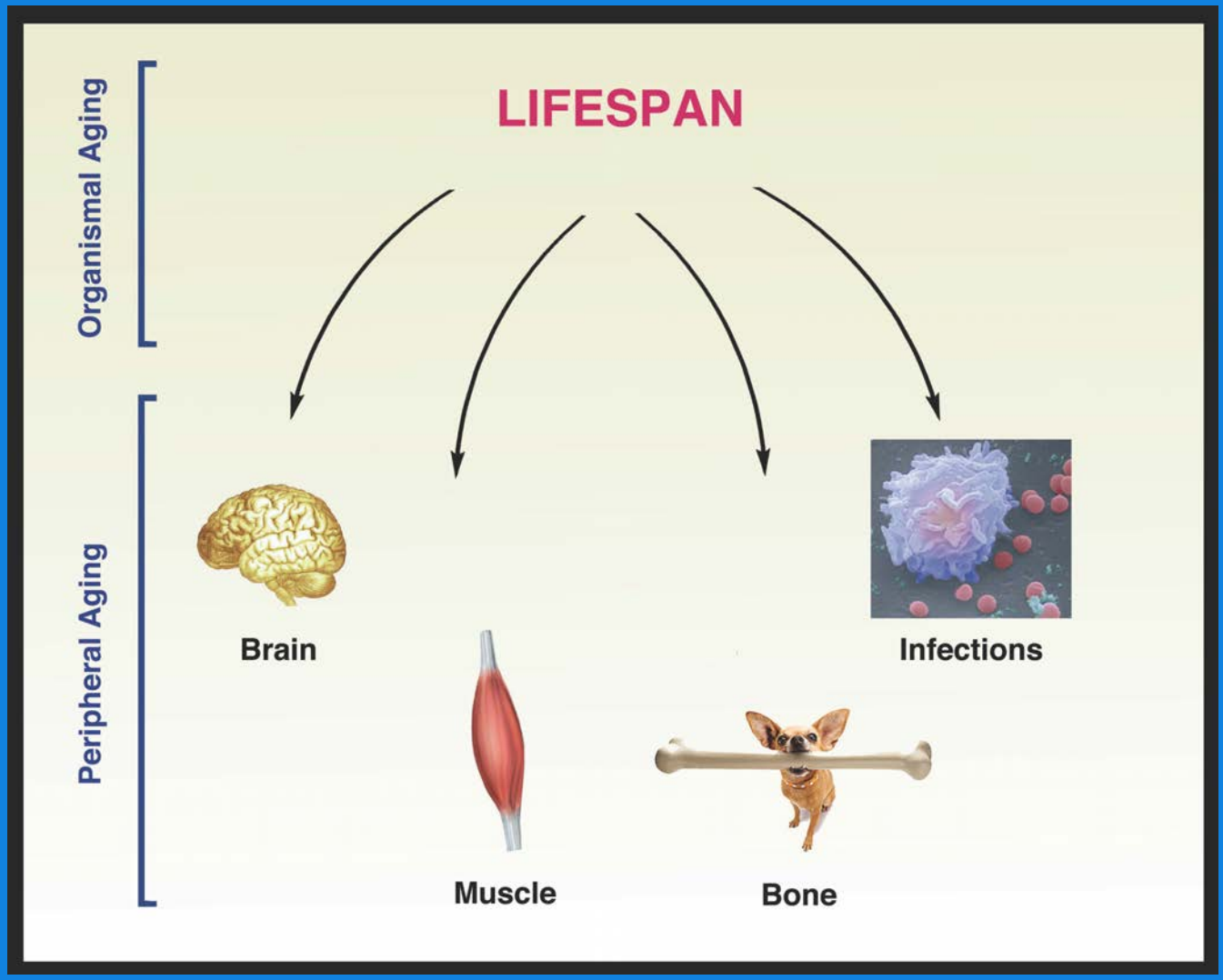




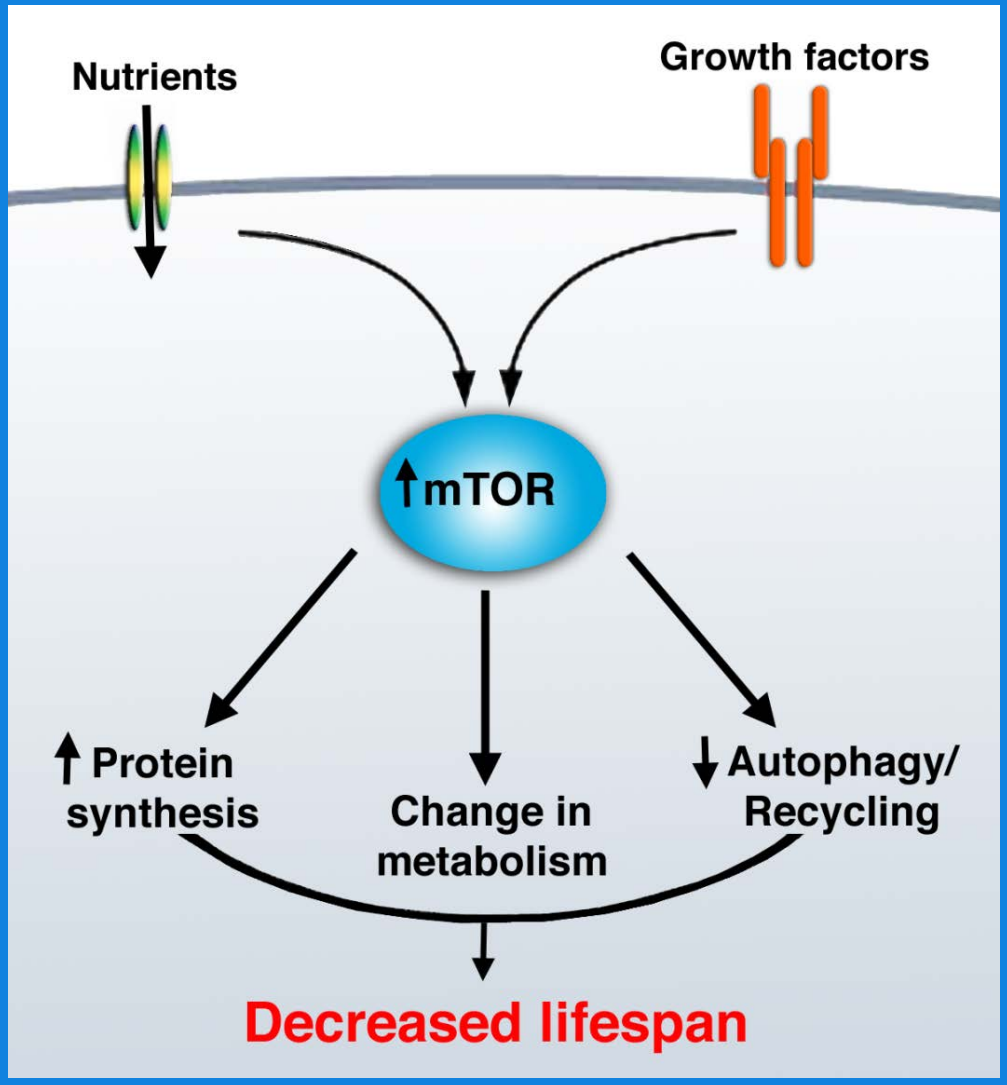
But…..mTOR$^{\Delta/\Delta}$ mice have higher rates of infection and increased age-dependent loss of bone density



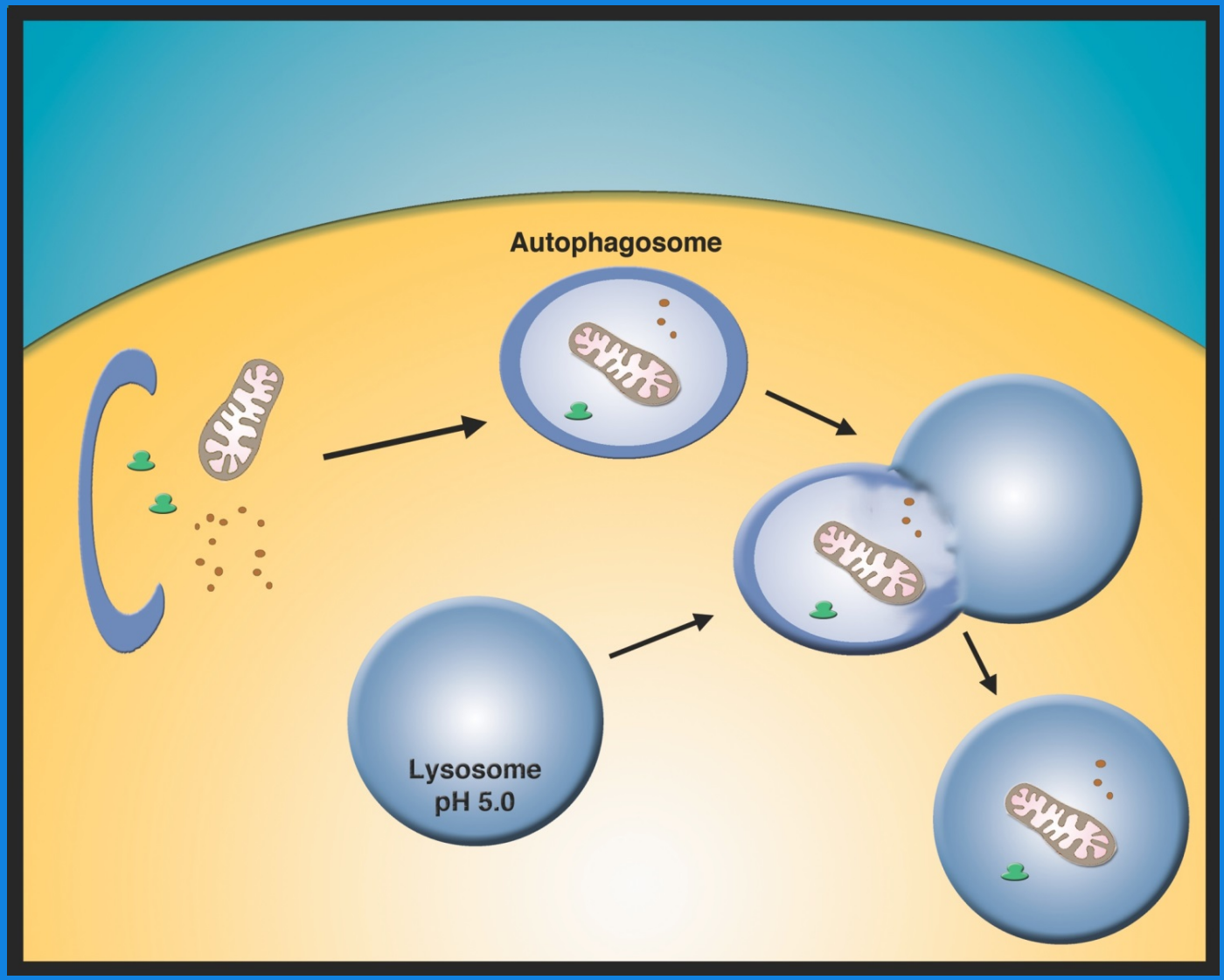
Central versus peripheral aging: Do our body parts age at different rates?



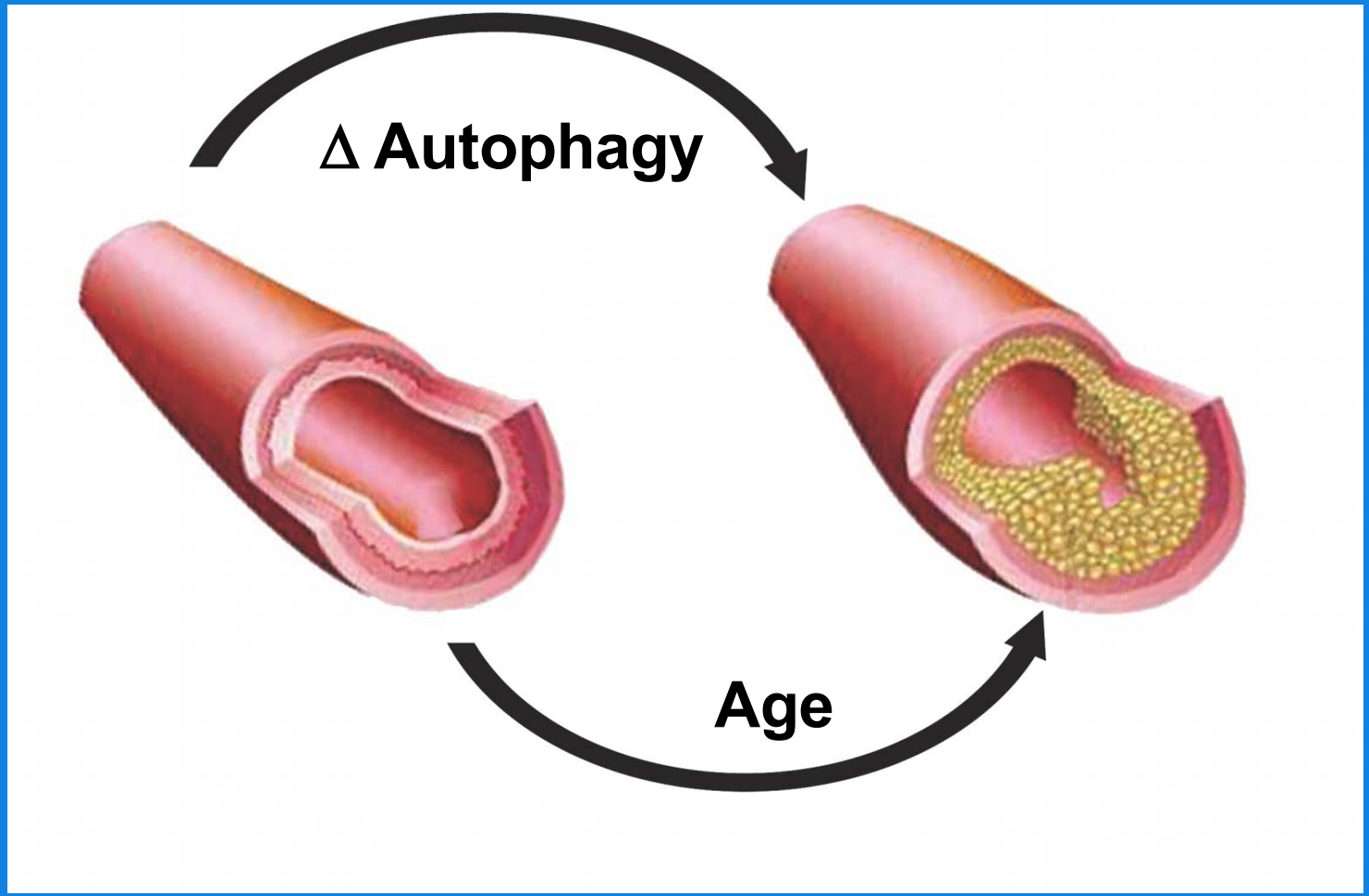
The mTOR pathway links nutrients to lifespan



Autophagy as an intracellular recycling system



Can the absence of autophagy recapitulate vascular aging?

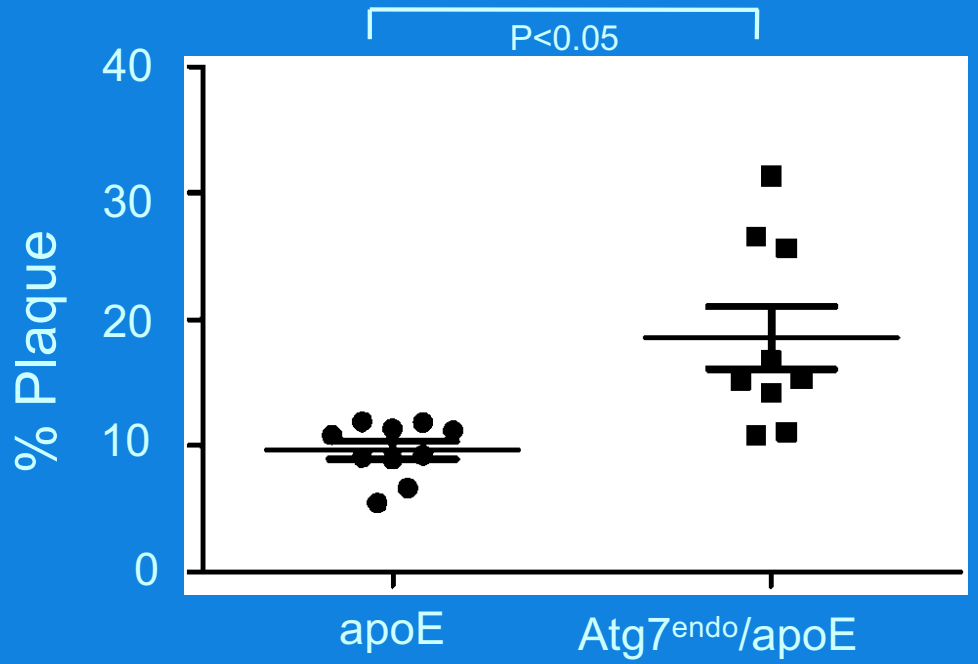


Atg7 deficiency in endothelial cells accelerates atherosclerosis

A

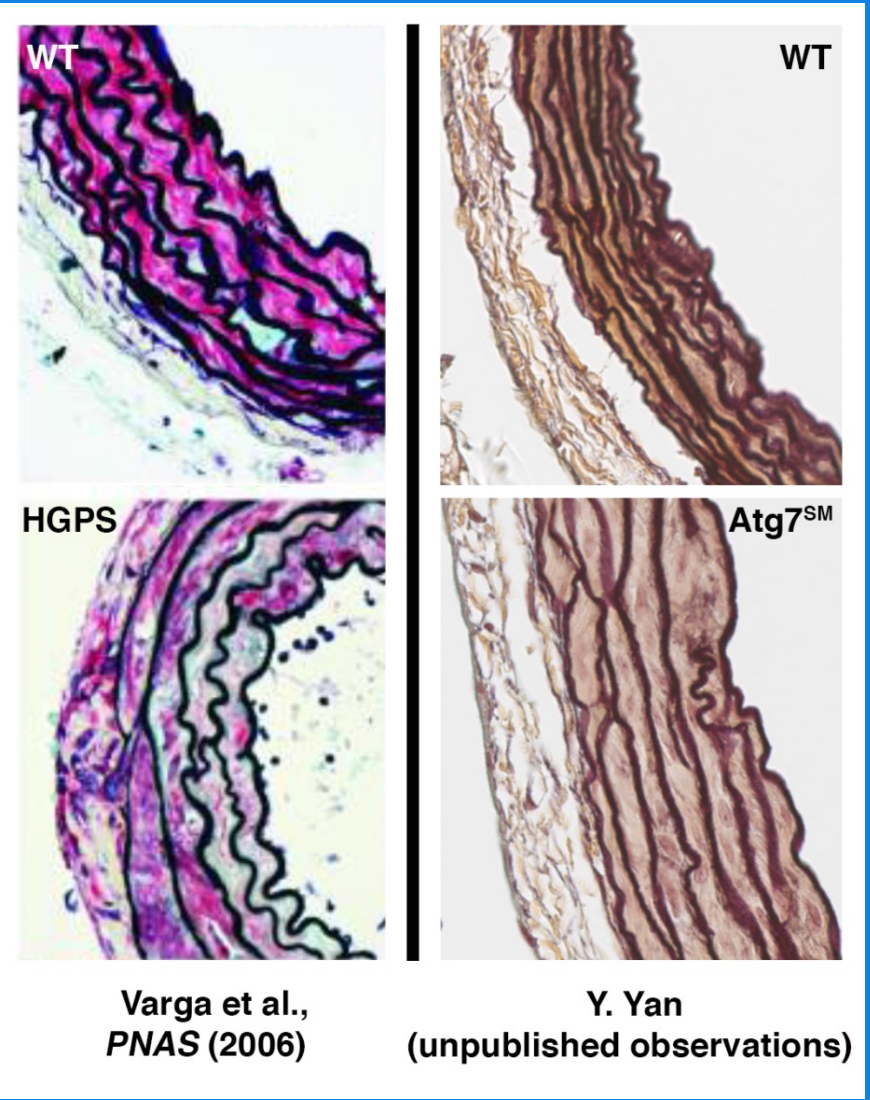
apoE Atg7^{endo}/apoE

B

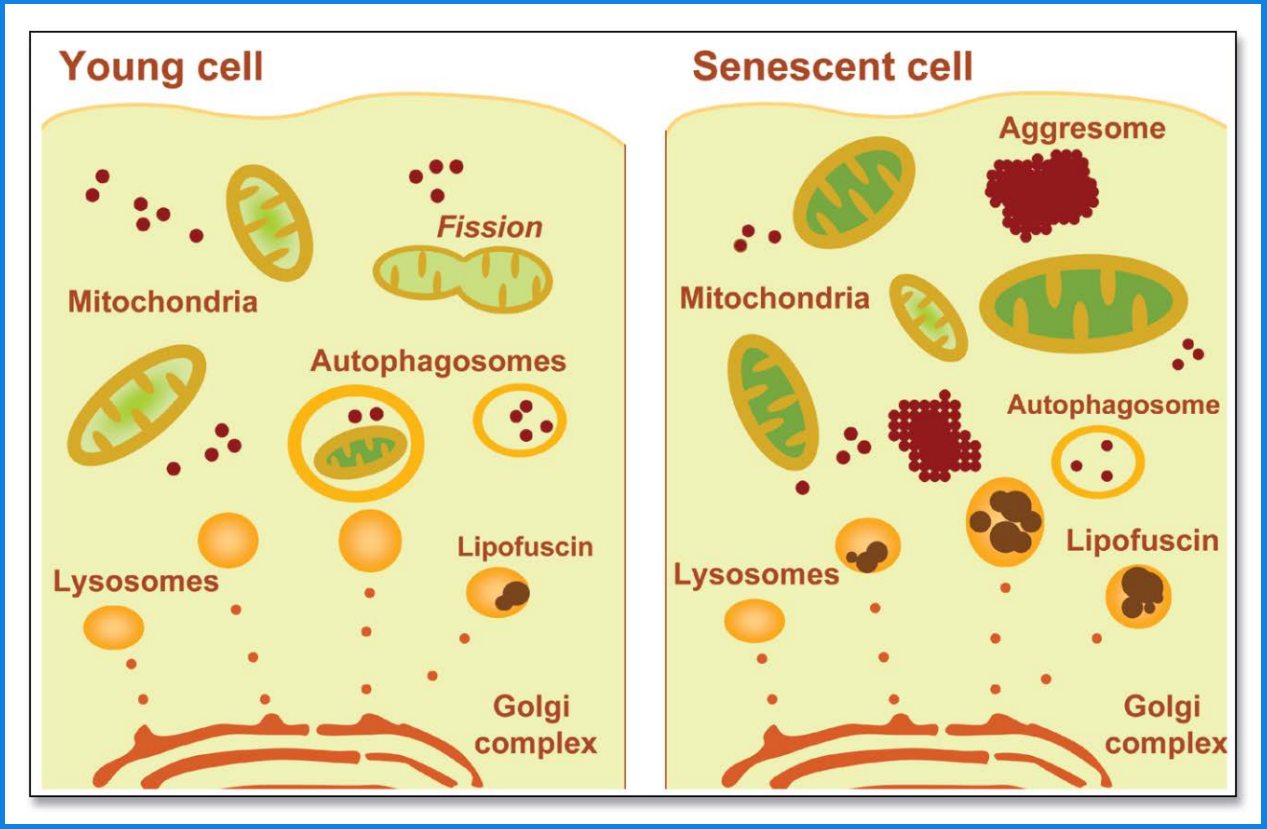


Torisu et al., *Aging Cell*, (2016)

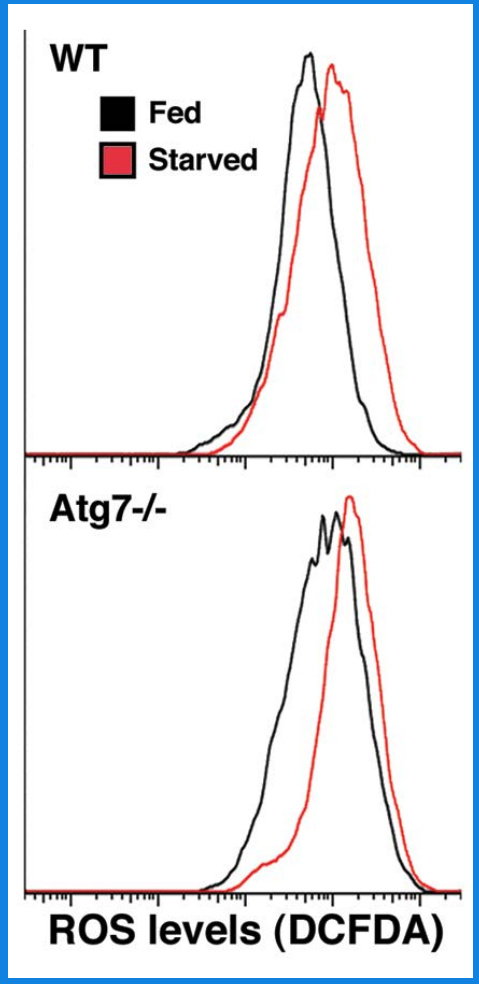
Does genetic deletion of autophagy in smooth muscle phenocopy HGPS?



Autophagy declines as cells and tissues age

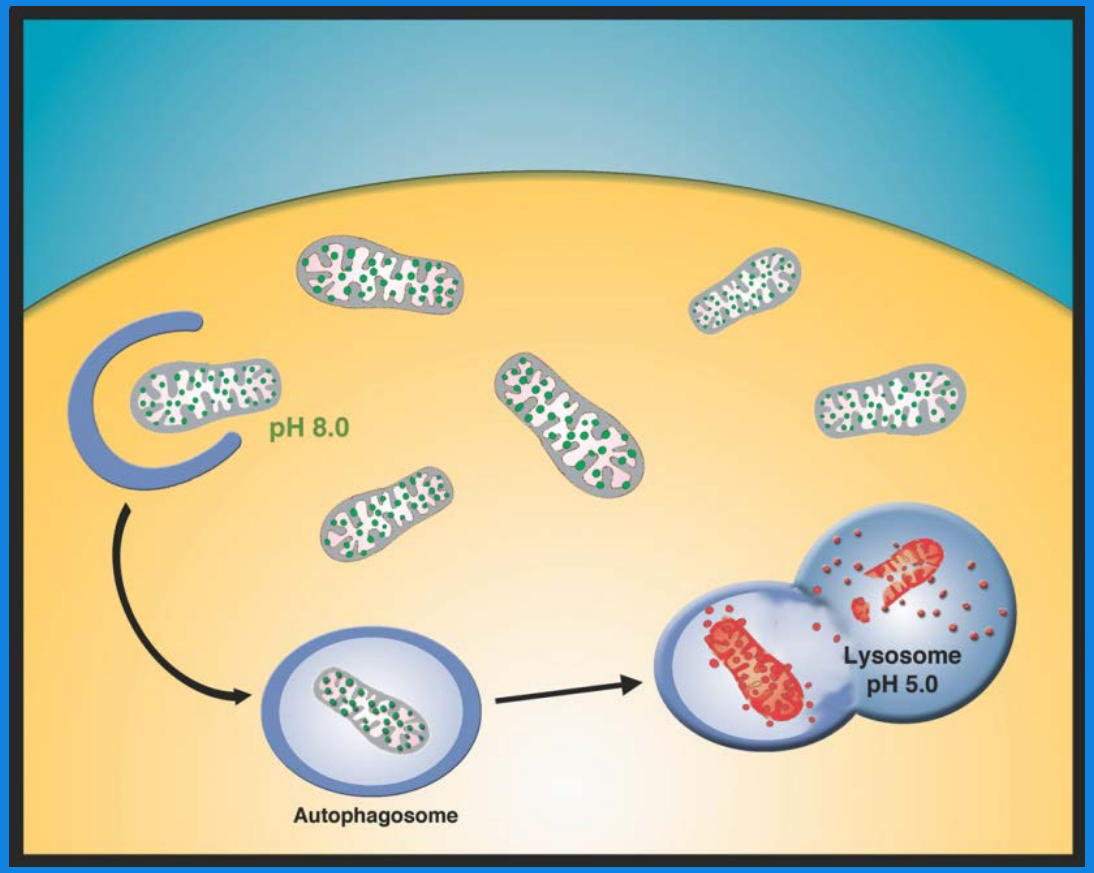


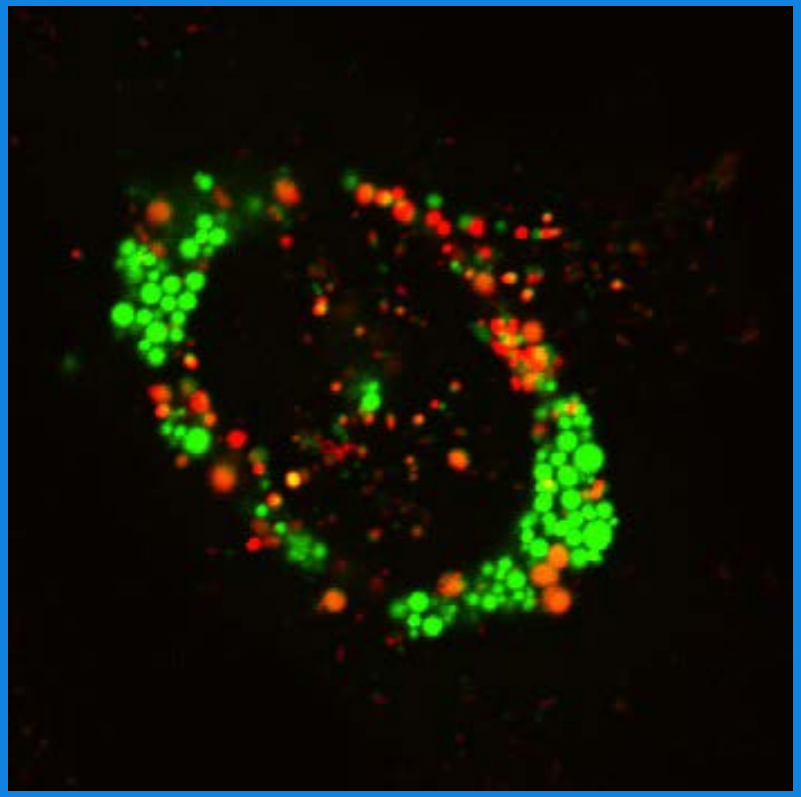
Cuervo et al., *Autophagy* 2005



Lee et al., *Science* (2012)

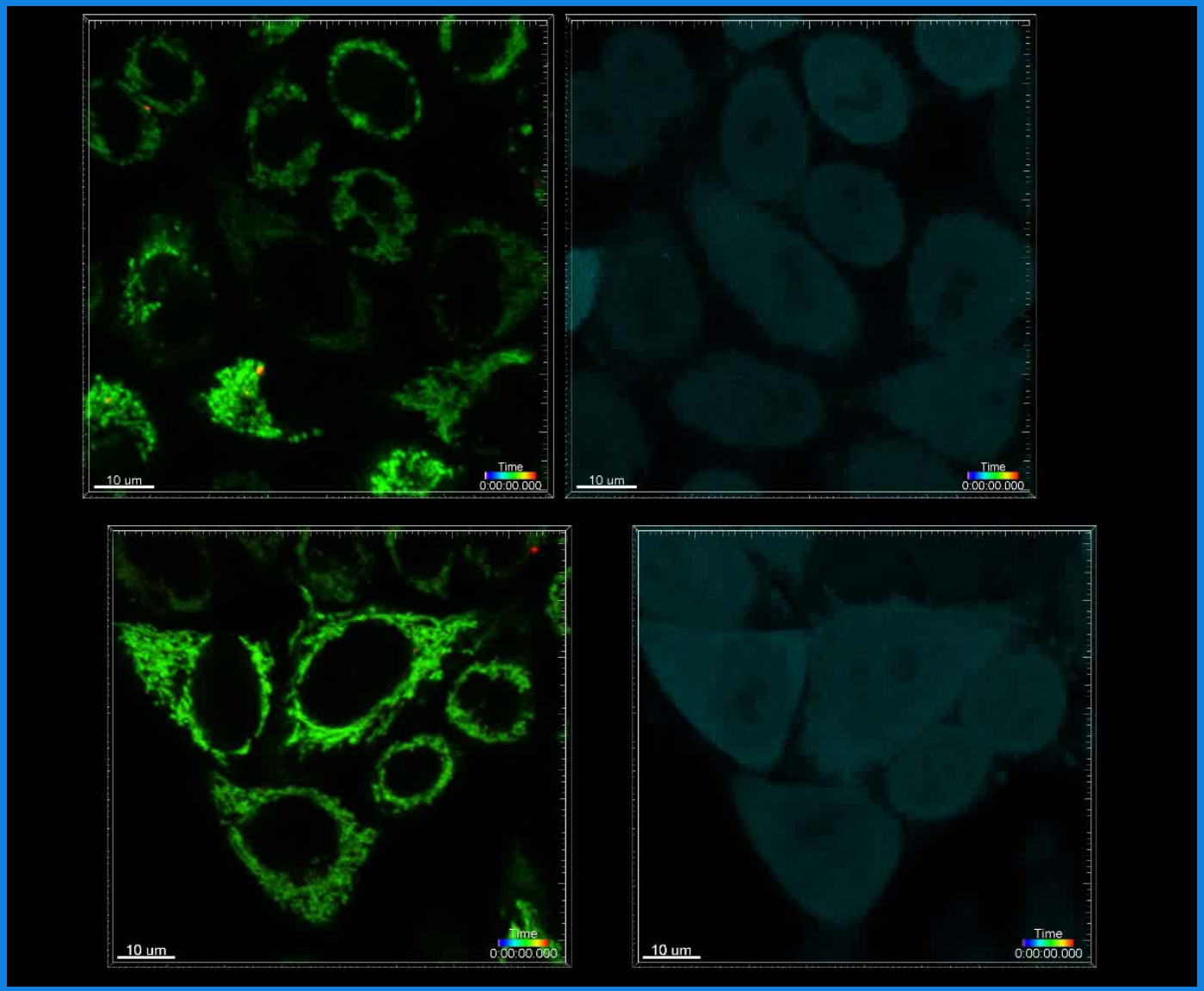
mt-Keima: A fluorescence based assay for mitophagy



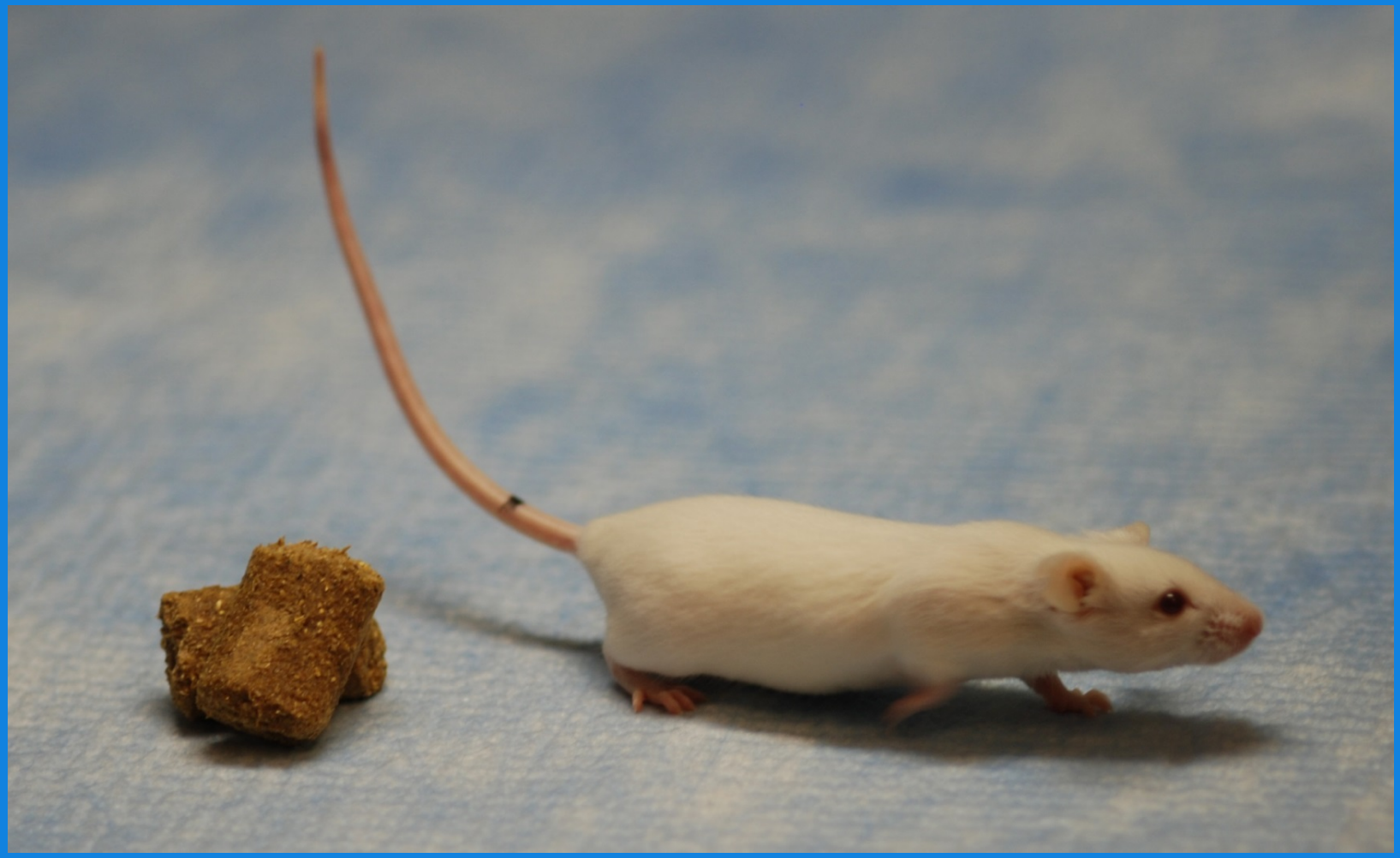


Adapted from Miyawaki and collaborators

Time-lapse Hela mt-Keima/YFP-Parkin

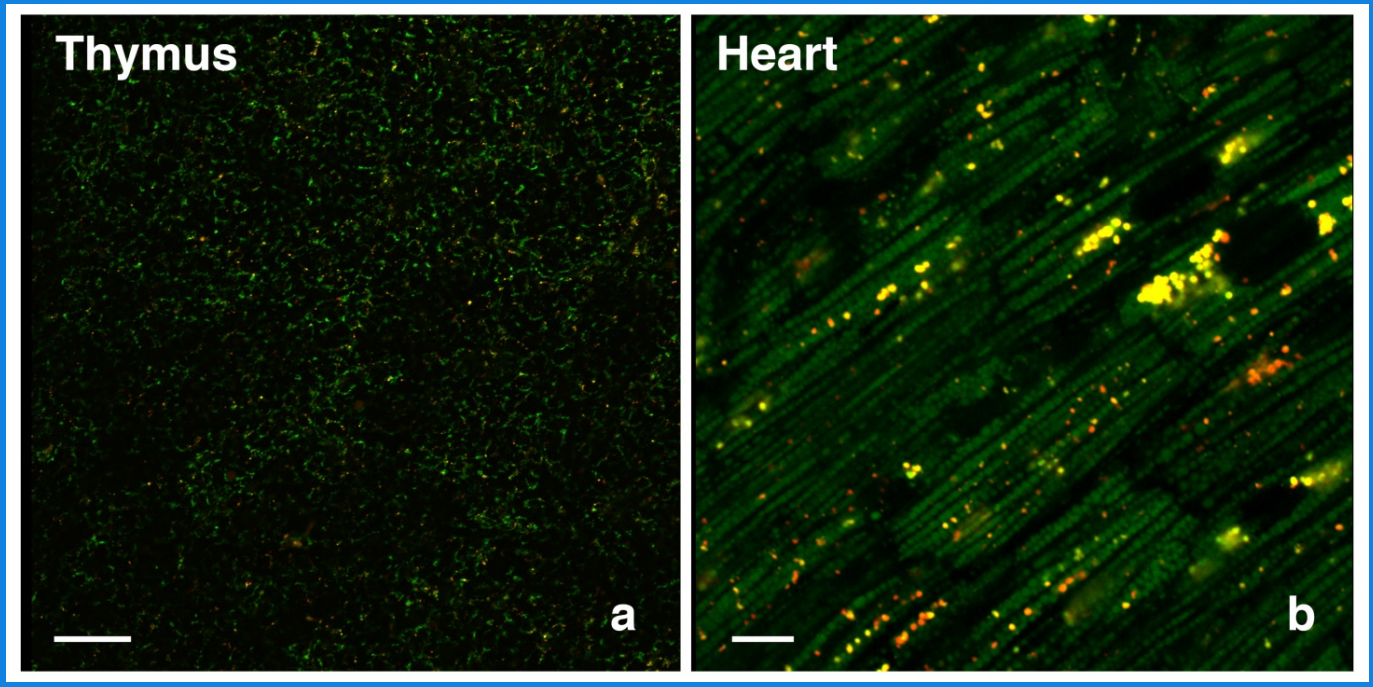


Transgenic Mouse Expressing mt-Keima

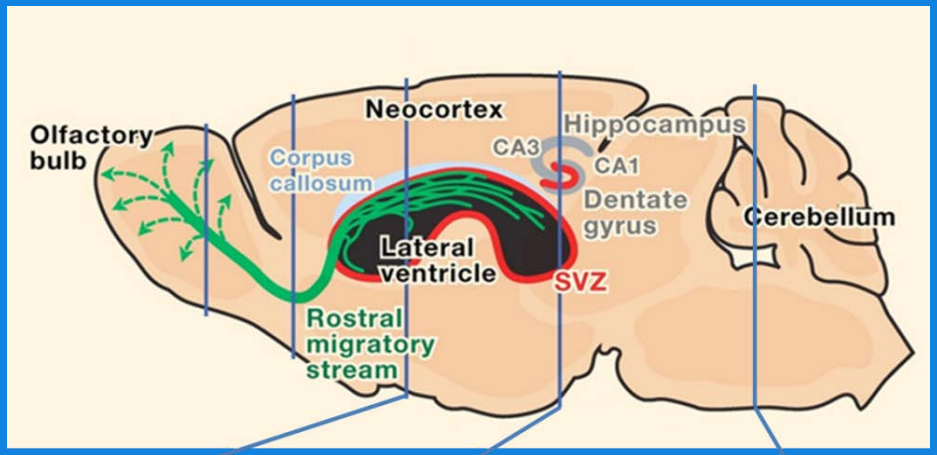


Sun et al., *Mol. Cell*, 2015

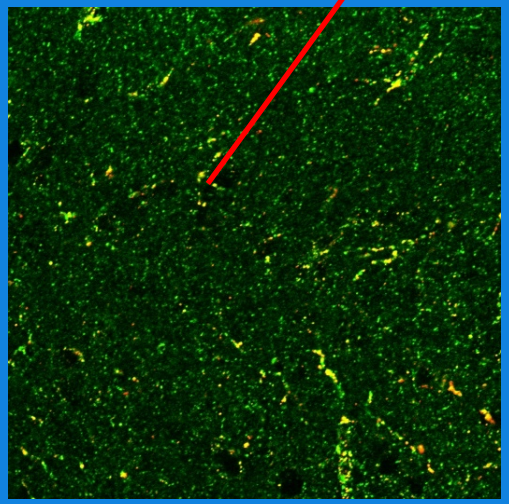
Tissues exhibit wide variation in mitophagic flux



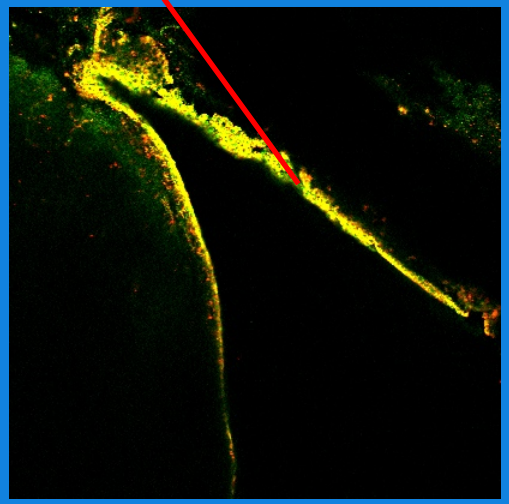
High rates of mitophagy in areas of resident adult stem cells



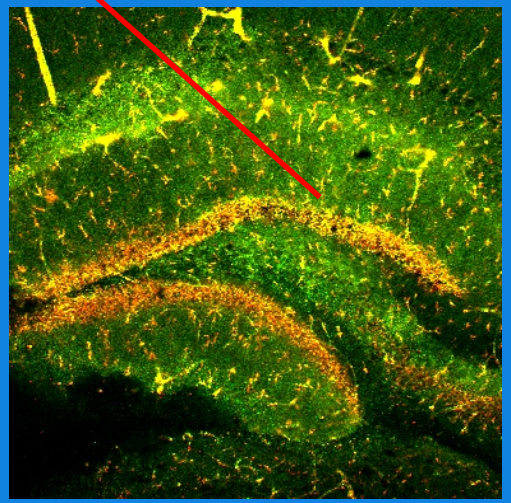
Cortex



LV



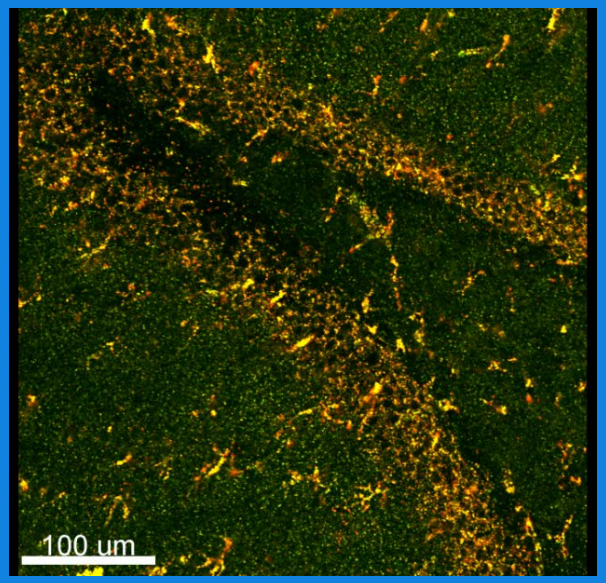
SGZ

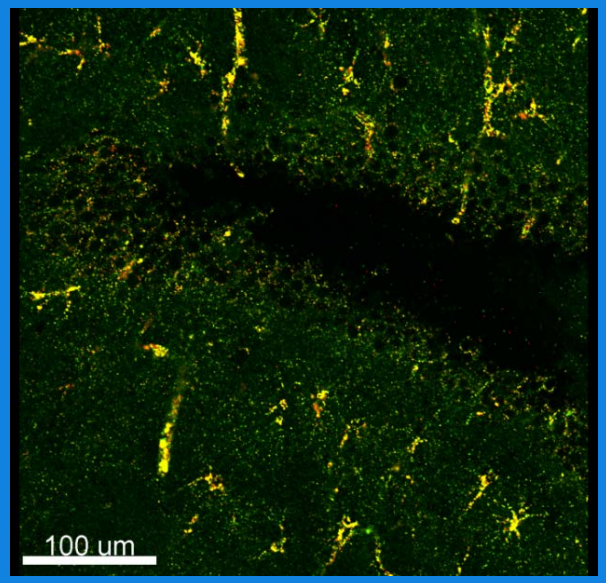


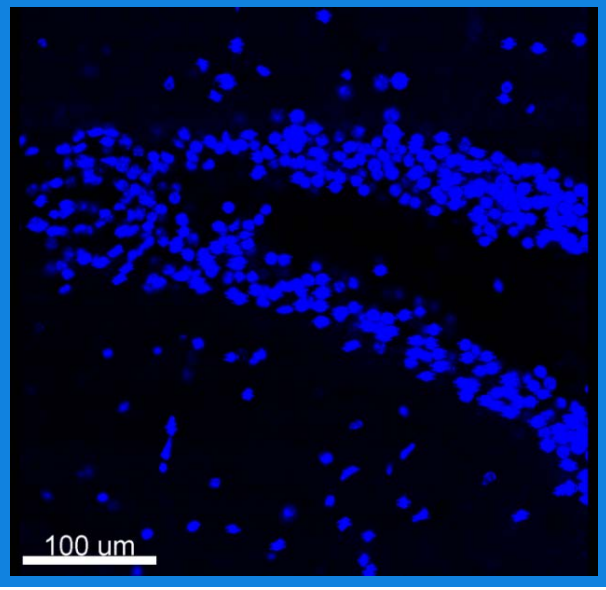
Age-dependent decline in mitophagy (SGZ)

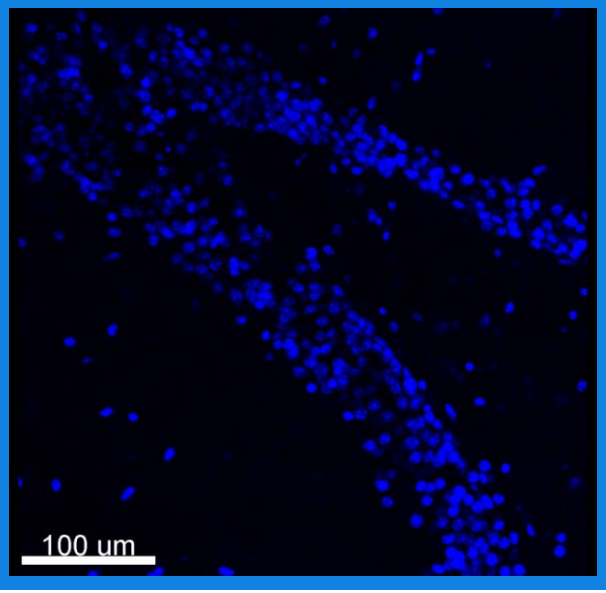
Young

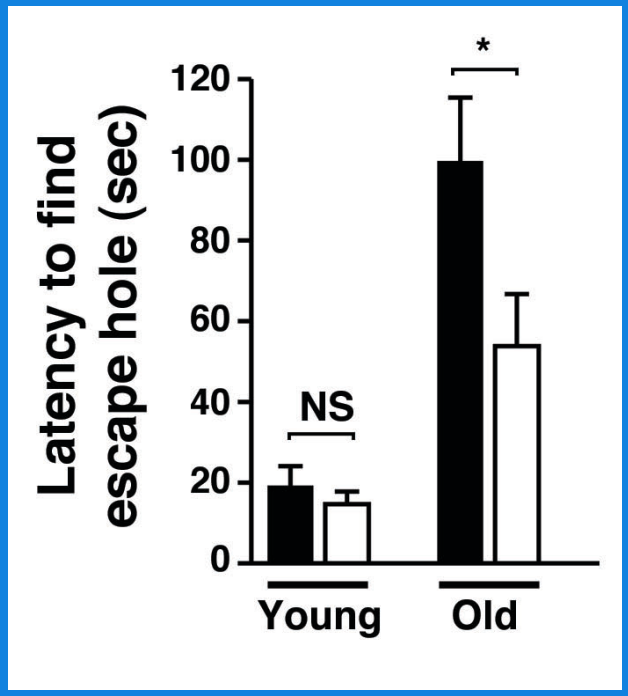
Old





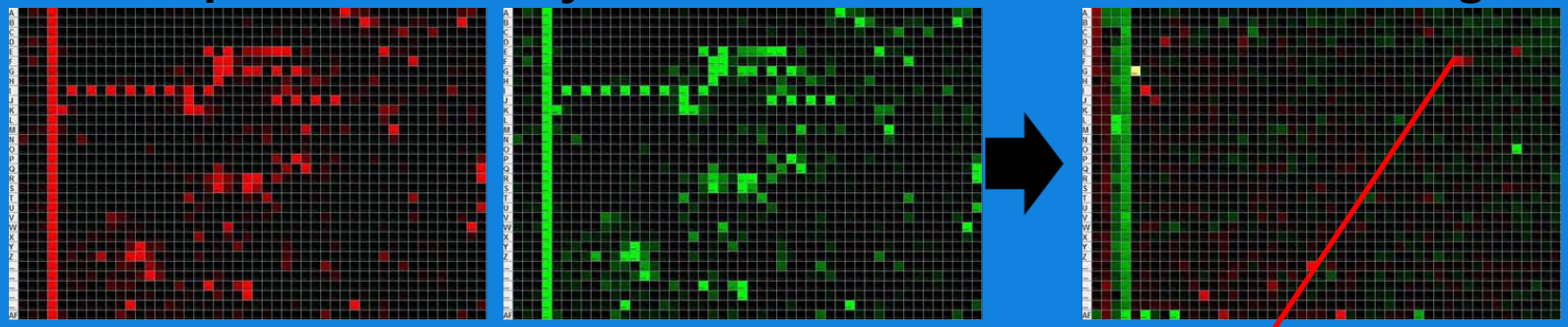






Chemical screen for mitophagy inducers

Heat Map View of Assay Plate from LOPAC HTS: mtKeima signal



3,000+ Small Molecules from NCATS FDA-approved library

High content image based screening

"HITS" (40)

Secondary Screening (20)

WB validation (18)

"MOA"

"SAR"

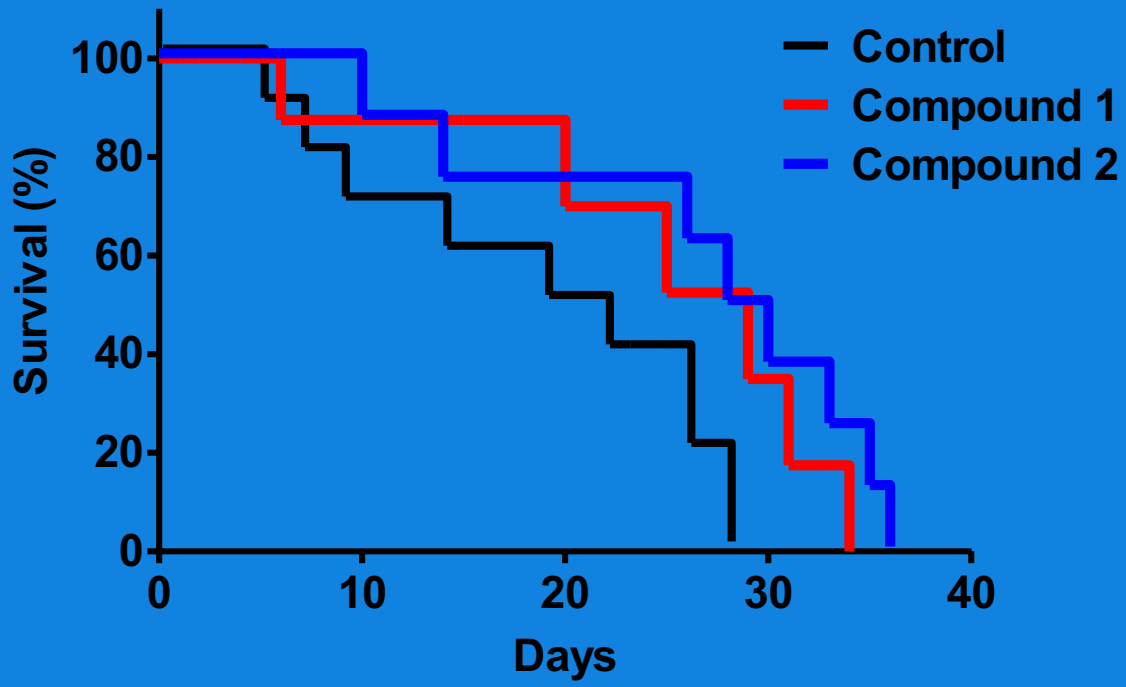
NSC self renewal

Insulin secretion

In vivo

Flies model *(Dr. Hong Xu)*

Preliminary results in a PINK1 fly model of Parkinson's disease



N. Sun, unpublished observations

Summary

Altering the rate of aging may alter when a wide range of age-related diseases manifest themselves.

Pharmacological approaches to slow aging may function as a set of ‘orthogonal’ treatments for a number of age-related diseases.

Acknowledgements

LAB MEMBERS:

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Yonghong Shi
Xuefeng Zhu

Beverly Mock (NCI)

Julie Wu (USPTO)